Updated Oleic Acid raw material specifications are enclosed as page 001. Revisions include the designation of the material grade as "BP/NF" and the elimination of the test codes which identified an internal method for the analysis.

2. **On page 313, you stated that the information regarding extractables from gaskets is contained in DMF Such information is not found in the referenced Drug Master File. Please provide this information.**

has indicated that they have filed a new DMF (DMF for valve gaskets) which incorporates information on extractables from the gaskets. A new DMF authorization letter for DMF is attached (page 002). Specific pages relevant to the valves and gaskets used for the drug product are identified in the authorization letter.

3. **We have the following comments regarding the dosage form laboratory controls:**
   a. **Please validate your assay method for its capability as a stability-indicating method and provide your results.**

The validation of the assay method as a stability-indicating method is enclosed as pages 003-044. Information concerning specificity of the method is contained in Section 8 of the report entitled Finished Product Validation Report For Albuterol Metered Dose Inhalation Aerosol Albuterol Assay (pages 015-017).

   b. **Please set limits for the in-process test for determination of shot weight as performed during the filling operation.**

Limits for the in-process test for determination of shot weight have been established as 77-90 mg/dose. The revised Quality Control Document - Filling incorporating these limits is enclosed as pages 045-047. Additional revisions include elimination of extraneous language in the In Process section. Part numbers were revised in the Component Specification section and the quantity per tray was changed from 256 to 225. The Quality Control Actions To Be Performed section was updated with current terminology and a section for weight of valves was added. The Quality Control Record Sheet was revised to include the dose weight and the documentation of product temperature. The number of units per tray was revised as was done for the Component Specification section.

c. **Please revise your drug product release specification to include the following:**
   i. **Metering Performance per Supplement # 9 to USP XXII <601>.**
   ii. **Microbial Limit Test.**
   iii. **Unit Spray Content.**
   iv. **Assay for the drug substance content in the entire canister.**
   v. **Spray Pattern.**
   vi. **Albuterol Related Substances (Total and Individual).**

Please set your specifications for the above tests and submit revised release specifications for the finished dosage form. Please also provide the analytical methods and validation as appropriate for the new tests.

The drug product specifications have been revised to include the requested tests (pages 048-049).

Unit Spray Content was previously and still is measured in the test for Content Uniformity. The test method is enclosed as pages 073-076. On the Product Specification sheet (page 048), the "Shot Number" for analysis at the end of the can was changed from to "196-200" to correct a typographical error. Five actuations are used for the analysis, as illustrated in the beginning testing (10-14) and the middle testing (100-104).

In addition, a test for Can Content Weight (Content of Salbutamol) has been added for increased control of the drug product. The test method for Content of Salbutamol (Can Content Weight) is enclosed as pages 115-116.

A test for Particle Size by Cascade Impaction has been added and the test for Particle Size by Laser was deleted since it was a redundant test to the Cascade Impaction test. The test method for Particle Size by Cascade Impaction is enclosed as pages 164-167.

Please note that test methods for release testing and stability testing have different method numbers, though in fact they are actually the same method.

Test	Release Method No.	Stability Method No.
Uniformity of Unit Spray Content, Through the Actuator (Content Uniformity; Unit Spray Content)	✓	✓
Related Substances		
Content of Salbutamol (Can Content Assay)		
Particle Size by Cascade Impaction		

The analytical test methods and methods validation are provided as follows:

Metering Performance (page 051).

Methods validation was not performed for Metering Performance since the test does not lend itself to validation and since it is a compendial test.

Microbial Limit Test (pages 053-068 and 069-071, respectively).

Content Uniformity [Uniformity of Unit Spray Content, Through The Actuator (Unit Spray Content)] (pages 073-076 and 077-109, respectively).

Methods validation for the Content Uniformity method was previously submitted as pages 499-530 of the 2/4/94 amendment (pages 077-109 of this amendment). Please note that the method was revised to provide for testing at the end of the canister (ie., sprays 196-200) rather than the previously tested sprays (pages 073-076). In addition, reference to the internal SOP for calculations was deleted since the formula for the calculations is provided and Appendix 1 was assigned page number 4 of 4 whereas previously it was un-numbered.

The stability procedure previously submitted as pages 516-519 of the 2/4/94 amendment (pages 093-096 of this amendment) has been revised to provide for testing at the end of the canister (ie., sprays 196-200) rather than the previously tested sprays In addition, the name of the procedure was changed from to Uniformity Of Unit Spray Content Through The Actuator" in order to be consistent with the release procedure name. The SOP referenced for calculations (ie., was changed to RCa-01-XX as a means to reference the current procedure. The previous "01" suffix

indicated the first revision, while the current "XX" suffix stands for the current revision, regardless of its number. The revised procedure is provided as pages 110-113.

Can Content Assay (Content of Salbutamol) (pages 115-116 and 003-044, respectively).

Methods validation is provided as pages 003-044 in response to observation 3a which requested validation of the assay.

Spray Pattern (page 118).

Methods validation was not performed for Spray Pattern since validation is impractical and not meaningful.

Related Substances (Individual and Total) (pages 120-121 and 122-160, respectively).

Methods validation for the Related Substances method was previously submitted as pages 531-570 of the 2/4/94 amendment (pages 122-160 of this amendment). Please note that the Related Substances method number for stability testing is and the method number for product release is The methods for stability and release are the same.

d. Please revise your specification for Leakage Test in accordance with Supplement # 9 to USP XXII <601>.

The specification for Leakage Test has been revised to comply with the test in accordance with Supplement #9 to USP XXII <601> (page 049).

e. Please submit a revised certificate of analysis for your bio/stability batch including all the tests recommended above.

A new Certificate of Analysis for the bio/stability batch (batch #6403) incorporating the additional tests is enclosed as page 161. This new Certificate of Analysis was developed based on retesting of the drug product prior to use of the batch in the bio-study. The new Certificate of Analysis contains test results for the tests suggested in the document *Albuterol Metered Dose Inhalers: Development Of In Vitro and In Vivo Bioequivalence Standards For Generic Formulations,* prepared by W. Adams, et. al. of CDER, FDA.

A copy of the Certificate of Analysis previously submitted as page 380 of the 2/4/94 amendment is enclosed as page 162 since it contains results from additional tests. This previous Certificate of Analysis was developed based on the initial testing of the drug product.

f. **We note that you evaluate the particle size distribution by Laser Diffraction Method. We request that you conduct particle size distribution by a second method - Cascade Impactor based on the method described in Supplement # 9 to USP XXII. Please submit a description of your method and its validation with proposed specifications.**

A Cascade Impactor test method has been instituted as a test method for particle size determination of the drug product. The Cascade Impactor test method and methods validation are enclosed as pages 164-167 and 168-211, respectively. A specification of AMMD (aerodynamic mass median diameter) μm has been established for drug product release (page 048). The Laser Diffraction Method has been deleted since it is redundant to the Cascade Impaction Method. Since particle size affects deposition characteristics of albuterol in an aerosolized spray, the drug product is monitored for Deposition of Emitted Dose by use of a Twin Impinger apparatus. This test monitors the quantity of drug deposited in the Stage 2 section of the Twin Impinger apparatus and thus determines the availability of the drug as a function of particle size. Therefore, particle size is monitored by two methods.

g. **Please submit your method for the determination of the total number of actuations per canister.**

The test method for Total Number of Actuations Per Canister is contained within the analytical method entitled Uniformity Of Unit Spray Content, Through The Actuator (test code). This test method was previously submitted as pages 362-365 of the 2/4/94 amendment. The method is being resubmitted as pages 073-076 in response to observation 3ciii which requested the method for Unit Spray Content. The method for the number of actuations per canister is detailed in the Sample Preparation section, steps 1-8 (page 074).

4. **We have the following comments regarding the stability of the drug product:**

   a. **Please revise your stability testing protocol to include final specifications for the content uniformity and extractables.**

   The stability testing monograph and protocols have been revised to include final specifications of % of label claim for Content Uniformity and Not More Than % w relative to albuterol for extractables. Additional revisions are noted along with the protocols.

   Stability Monograph (pages 212-214).
   Pre-Approval Stability Protocol, 40°C, Inverted Orientation (pages 216-219).
   Pre-Approval Stability Protocol, 25°C, Inverted Orientation (pages 221-224).
   Pre-Approval Stability Protocol, 40°C, Upright Orientation (pages 226-227).
   Pre-Approval Stability Protocol, 25°C, Upright Orientation (pages 229-230).
   Post-Approval Stability Protocol, 25°C, Inverted Orientation (pages 232-234).

   b. **Please revise your post-approval stability testing protocol to include tests for can content assay, can content weight, spray pattern, related substances (individual and total), and the Microbial Limit Test. Furthermore, a reasonable effort must be made to chemically identify the major impurities formed over the shelf life of the drug product.**

   The post-approval stability protocol has been revised to include tests for Can Content Assay, Can Content Weight, Spray Pattern, Related Substances (Individual and Total), and the Microbial Limit Test (pages 233-234).

   Identification of the major impurities formed over the shelf-life of the drug product has been attempted and the impurities are monitored throughout the stability study. Methods validation for the Related Substances method was previously submitted as pages 531-570 of the 2/4/94 amendment (pages 122-160 of this amendment). The Introduction section of the validation report entitled Albuterol/Salbutamol Finished Product Related Substances Validation Report identified the major related substance as 1-(4-hydroxy-3-methylphenyl)-2-Tert Butylamino) ethanol (page 123). This compound is referred to as the "ethanol impurity". Please note that the Related Substances method number for stability testing is and the method number for product release is . The methods for stability and release are the same.

c. Please submit results of temperature cycling studies conducted for the exhibit batch in accordance with the CDER Stability Guideline.

Temperature cycle studies for this drug product were previously submitted as pages 006 and 015-021 of the 7/5/90 amendment (pages 235-242 of this amendment). Since a temperature cycling study for this drug product formulation has already been submitted to the application, it is not necessary to resubmit a new study. The executed batch record (Manufacturing Document) for the cycled batch [batch #0291E1 (listed as batch 291)] previously submitted as pages 010-015 of the 4/23/90 amendment is enclosed as pages 243-248 of this amendment to demonstrate comparability with the drug product formulation contained in the current Manufacturing Document (pages 265-273).

d. We note that you evaluate the particle size distribution by Laser Diffraction Method. We request that you conduct particle size distribution for the drug product by a second method - Cascade Impactor based on the method described in Supplement # 9 to USP XXII. Please submit validation of the method and propose specifications.

A Cascade Impactor test method has been instituted as an additional test method for particle size determination of the drug product. The Cascade Impactor test method and methods validation are enclosed as pages 182-185 and 168-211, respectively. Specifications of MMAD (mass median aerodynamic diameter) μm have been established for stability testing of the drug product (page 233). Please note that the Particle Size by Cascade Impaction test has been added as an additional test for the pre-approval room temperature inverted orientation) stability study and has replaced the Laser Diffraction Method for the post-approval stability studies. The pre-approval room temperature stability study will continue to monitor particle size by the previous Laser Diffraction method and will institute the additional Cascade Impaction method for the remaining stability test stations (ie., 12, 18, and 24 months). Since particle size affects deposition characteristics of albuterol in a aerosolized spray, the drug product is monitored for Deposition of Emitted Dose by use of a Twin Impinger apparatus. This test monitors the quantity of drug deposited in the Stage 2 section of the Twin Impinger apparatus and thus determines the availability of the drug as a function of particle size. Therefore, particle size is monitored by two methods.

5. **Please submit a signed certification stating that the facilities of CCL Industries, England are operated in compliance with all the appropriate environmental laws and regulation.**

   A signed certification from CCL for compliance with all appropriate local environmental laws and regulations is enclosed as page 249.

6. **Bioequivalency of the proposed product has not been demonstrated. Please note that a new Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers) was issued on January 27, 1994.**

   Bioequivalency of the drug product will be demonstrated based on the Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers) (issued on January 27, 1994). The bioequivalency study is underway and results will be submitted upon completion of the study.

B. Labeling Deficiencies:

The labeling has been revised as requested. Final printed container labels, carton labeling, and insert labeling are enclosed as follows:

Container labeling (page 251).
Refill container labeling (page 253).
Carton labeling (page 255).
Refill carton labeling (page 257).
Insert labeling (pages 259).

In addition to providing the above responses, A.L. Laboratories also notes and acknowledges the following:

1. **The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.**

   A.L. Laboratories acknowledges that all the facilities listed in the application must be in compliance with CGMPS at the time of approval of the application.

2. **Please be advised that samples of the drug product will be requested for methods validation at a later date after the testing issues are resolved.**

   A. L. Laboratories acknowledges that samples of the drug product will be requested at a later date.

3. **Please submit any additional room temperature stability data that may be available.**

   The additional room temperature stability data through the 12 month test station is enclosed as follows:

   Inverted storage orientation (pages 261-262).
   Upright storage orientation (page 264).

Additional Revised Documents

A revised MPCR (Manufacturing Document) is enclosed as pages 265-273. Revisions include updates in the Precautions section, Cleaning Record section, Pre-Manufacturing Checklist section, Manufacturing Calculations section, and Manufacturing Adjustments section. No material changes occurred in these sections. The sections were changed to provide increased instructions and to incorporate current SOPs and terminology. The Manufacturing Procedure section was also updated with current terminology. Step[revised to specify

]to provide increased control of the process (page 270).

The in-process test specifications (Quality Control Analysis Sheet Bulk Intermediate) pages were revised to specify "SOP AN36" rather than[ ]for the determination of water content (pages 274-276).

A revised Filling Document is enclosed as pages 277-288. The Filling Specification section was revised to include additional part numbers and to change existing part numbers. The Precautions section was revised to include additional SOP references and to provide additional instructions. A new Start Up Line Clearance section has been added for increased control of the process. The Engineering Set Up section was revised to include documentation of environmental temperatures. The Line Set Up section was revised to incorporate current practices. A new Q/C Approval To Commence Filling section was added to provide increased control of the process. The Line Operators section was revised by deleting reference to attaching records of labeling on a later page.The Reconciliation section was revised to include documentation of the final sequential can number and to document the name of the individual performing component

reconciliation. C/Weigh/Count and Mach/CT O/T were deleted since they are incorporated in all C/Weigh/Rejects. The Bulk Reconciliation section was revised to include manufacturing reconciliation. Updated terminology was added throughout. The Line Clearance Certificate section was revised with updated terminology (ie., "product" changed to "filled units"; "in good order" changed to "tidy"). The Record Sheet For The Best Checkweigher Weight Checks section was revised so that weight checks are performed at 15 minute intervals rather than at 30 minute intervals. Weight limits were added for increased control of the process. Tare weight documentation was also added.

A revised raw material specification for albuterol drug substance (Salbutamol/Albuterol BP/USP/EP) is enclosed as pages 289-290. Revisions include the addition of the Boron test for compliance with the European Pharmacopeia (EP) and inclusion of EP in the designation of the grade of material in the product name. Additional requirements for the Certificate of Analysis from the manufacturer have been added for increased control. The test codes which identified an internal method for the performance of tests have been deleted.

A revised Packaging Material Specification for the aluminum can is provided as pages 291-294. Revisions include the addition of a section entitled "Measurements" and the movement of physical measurements out of the "Major Defects" section and into the "Measurement" section. In addition, the "Brimful Capacity" test was moved from its own section and into the "Measurement" section.

A Packaging Material Specification for the aerosol valve has been created and is being submitted for the first time (pages 295-297). This specification is to be used in conjunction with the Incoming Component Inspection Test for the valve previously submitted as pages 314-319 of the 2/4/94 amendment (pages 298-303 of this supplement).

A.L. Laboratories certifies that a field copy of this amendment has been submitted to the FDA district office pursuant to 21 CFR 314.96.

We trust that this response has addressed the Administration's concerns.

Sincerely,
A. L. LABORATORIES, INC.
Ronald Bynum /for

Deborah Winkel
Sr. Director, Regulatory Affairs

Enclosure

ORIGINAL

A.L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

February 4, 1994

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

DR. Label
NDA ORIG AMENDMENT
AC

Re: ANDA #73-045
Albuterol Inhalation Aerosol

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Reference is made to the Administration's letter dated July 12, 1991 (attached) regarding the deficiencies of the Abbreviated New Drug Application dated December 23, 1988. The Administration's comments have been restated and A.L. Laboratories' responses follow. In addition, A.L. Laboratories Inc. is taking this opportunity to update the pending application with revised information resulting from the May 7, 1992 transfer of ownership of the application to A.L. Laboratories Inc. As noted below, CCL Industries Ltd., the contract manufacturer of the drug product, has assumed responsibility for analytical testing of the drug substance, inactive ingredients, and the drug product. Therefore, most of the responses to the pending deficiencies will be based on information concerning CCL's current practices. This submission consists of two volumes. (Volume I contains response letter up to page 358. Volume II contains pages 359-667).

1. **Please provide data to show that your assay method for the analysis of the drug substance is equivalent to the method found in the USP's monograph for the drug substance. The final results between the two tests might be different, since you determine the end point in the assay electronically, while the USP requires the use of crystal-violet for end point detection.**

RESPONSE:
The assay method adopted by CCL for the analysis of the albuterol drug substance is identical to the USP method. The assay method is enclosed as pages 35-45.

2. **Please explain why there was only one week of circular and X-Y humidity and temperature charts rather than the full six weeks of charts?**

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GENERIC DRUGS

The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500 • Baltimore, Maryland 21224
Tel: (410) 558-7250 • Fax: (410) 558-7262

RESPONSE:
The humidity and temperature charts on pages 007 to 014 of the 7/5/90 amendment were provided as representative data for the temperature cycling study, in lieu of submitting charts for the entire study. It should be noted that three weeks of charts were provided, not one week of charts.

3. **Please explain the large differences in median particle size diameters between the laser and the image analysis procedure, and the cascade impact method. Why shouldn't they almost be the same?**

RESPONSE:
The particle size methods adopted by CCL are different than those previously contained in the application. CCL's apparatus is being used rather than a Impactor.

CCL's Laser Diffraction Method (Malvern 2600c Laser) (pages 126-127 for drug substance and pages 373-375 for drug product) is used to determine the size of particles, while CCL's Deposition of the Emitted Dose method (Twin Impinger (pages 366-370) measures the quantity of albuterol deposited in the Stage 2 section of the twin impinger apparatus. Since the two methods are used to measure different characteristics of the aerosol, they therefore do not show equivalent results.

4. **Please explain the sharp rise for total impurities between the 19th and 22nd month from % of Lot 0291E1. Were these impurities ever identified and does any one of them correspond to the extracted peak at m/z and having a molecular weight of 186? Why wasn't this molecule identified?**

RESPONSE:
The Total Impurities Test of the Related Substances Test has been revised to CCL's Related Substances Test. Specifications of Less Than % Individual Impurities, and Less Than % Total Impurities have been established. The stability data discussed in response to Question 5 below indicates that batch #6403 of Albuterol Inhalation Aerosol meets the established specifications and there were no sharp rises in impurity levels during the study (pages 621 and 623).

Since CCL is performing the Related Substance Test with a different analytical method than was previously used, comments concerning test results from the previous method and from a different laboratory are no longer relevant.

Related Substances will continue to be monitored in the on-going stability studies being conducted by CCL.

5. Please provide all stability data accrued to date.

RESPONSE:
The stability data for a new batch of Albuterol Inhalation Aerosol, batch #6403 is enclosed as pages 618-635. This stability data was generated by CCL. Since CCL has assumed responsibility for stability testing and since some of the stability analytical methods have been changed, only the stability data generated by CCL is relevant to the application.

Labeling:

RESPONSE:
The labeling has been revised as requested by the Administration. Four copies of draft labeling are enclosed.

Label (page 01)
Carton (page 02)
Refill label (page 03)
Refill carton (page 04)
Insert (pages 05-06)
Actuator Embossing - (page 07)

Please note that Barre-National Inc., a subsidiary of A.L. Laboratories, is listed on the labeling as the drug product distributor.

In addition to the aforementioned responses, A.L. Laboratories is taking the opportunity to update this pending application with revised information resulting from the transfer of ownership of the application to A.L. Laboratories.

DMF Authorization Letters allowing reference by A.L. Laboratories:

DMF . CCL Industries Ltd.- production of the drug product (page 08).

DMF

DMF

DMF

DMF

DMF

DMF

List of Responsibilities (page 18-19) and CGMP Certification:

A.L. Laboratories Inc. (page 20).

CCL Industries Ltd. (page 21).

It should also be noted that A.L. Laboratories has a business relationship with for the drug product.

At this time we are withdrawing reference to as the US agent for this application. As noted in the June 8, 1990 amendment to this application, has also been withdrawn as the US agent for this application.

Current List of Component Sources (pages 24-25):

Raw Materials

Albuterol USP

Oleic Acid NF

Trichloromonofluoromethane NF (Propellant 11)
Please note that has been added as an alternate supplier of trichoromonofluoromethane (propellant 11).

Dichlorodifluoromethane NF (Propellant 12)
Please note that has been added as an alternate supplier of dichlorodifluoromethane (propellant 12).

Packaging Components

Aluminum canister

DF31 Metering Valve

Please note that the aerosol valve has been changed from a metered valve [code #V00020 (55318SLB)] manufactured by to a DF31/63 RCU CS 20 mm silver valve (manufactured by

Actuator

Please note that the actuator has been changed from a

manufactured by to a blue mouthpiece and a white dust cap manufactured by

Refill Cap

Raw Material Controls

Active Ingredient - Albuterol

CGMP Certification, with date of last inspection, from drug substance manufacturer (page 26).

Certificate of analysis from drug substance manufacturer for batch #930190 (unmicronized material) (page 27).

CCL's testing specifications (pages 28-45) and data for batch #001216 (manufacturer's batch #930190) including spectra and chromatograms for reference standards and test samples for batch #001216 (pages 46-75).

Analytical methods validation (pages 76-141).

Inactive Ingredients

CCL's Testing specifications and data and Suppliers' Certificates of Analysis (specifications and test results).

(Oleic Acid), batch #R5111 (pages 142-159).

Trichloromonofluoromethane (Propellant 11), batch #R5150 (pages 160-173).

Dichlorodifluoromethane (Propellant 12), batch #R5154 (pages 174-186).

Manufacturing and Processing Instructions

Blank Batch Records for Intended Production Runs (180 kg mix size, unit size, g total batch size).

Manufacturing instructions (pages 187-197).

Filling instructions (pages 198-212).

In-Process Specifications and Analytical Procedures.

Specifications (pages 213-214).

Analytical procedure (pages 215-218).

Copy of Executed Batch Record - lot #6403 (some records indicate batch #403, or ALB 6403, or #6403 - however, all records pertain to the same batch, only the nomenclature of the batch number is different), a 60 kg mix size, units size, g total batch size.

Manufacturing records (pages 219-225).

In-process analytical results (pages 226-228).

Filling/packaging records (pages 229-293).

Please note that some units were packaged with labeling (label, carton, insert) identifying the product as Salbutamol Aerosol Inhalation BP, 100 microgram per inhalation. This labeling was utilized in order to simulate actual packaging/labeling operations of production batches. This particular labeling will not be utilized for production batches. As noted previously, the proposed labeling for this product is enclosed as pages 01-07.

Container/Closure

Summary of Container/Closure System (page 294).

Container/Closure Testing and Technical Data Sheets, Specifications, Test Results and Certificates of Compliance.

Valve , batch #C1722

CGMP certification (page 295).

technical data sheets, including drawings (pages 296-313).

CCL's testing parameters (pages 314-319).

CCL's test data (pages 320-328).

Certificate of Conformity for batch #0644400000 (CCL batch #C1722) (page 329).

Can , aluminum), batch #001295

Since the can has not changed since the 12/23/88 application (pages 00355-00361) and the 8/28/89 amendment (pages 00045-0048), only updated technical information on the can is being submitted in this amendment. However, please note that the can was previously designated as cc capacity and it is now designated as a mL capacity can. mL represents the brimful capacity and cc represents typical "drug content" capacity.

drawing (page 330).

CCL's Packaging Material Specifications (pages 331-334).

CCL's testing specifications (pages 335-337).

CCL's test data (pages 338-340).

Certificate of Conformance for batch #65/19 (CCL batch #001295) (page 341-342).

Oral Inhalation Adapter and Dust Cap shaped blue homopolymer SM6100 with white dust cap), batch #001734.

CGMP certification (page 343).

CCL's testing specifications (pages 344-346).

CCL's test data (pages 347-351).

Certificate of Conformance for batch #2189 (CCL batch #001734) (page 352).

Refill Cap mm white Propathene homopolymer polypropylene cap), batch #001433

drawing (page 353).

Technical Information Sheet for Propathene homopolymer polypropylene (page 354).

CCL's testing specifications (pages 355-357).

CCL's Goods Received Note for batch #001433 (page 358).

VOLUME II

Controls for the Finished Dosage Form - Albuterol Inhalation Aerosol

Testing Specifications and Data

Specifications (pages 359-360)

Analytical Methods (pages 361-378)

Analytical Results (pages 379-380)

Methods validation including stability-indicating test data of samples subjected to various stress conditions (pages 381-570).

Stability of Finished Dosage Form

Stability Specifications (pages 571-573)

Stability Protocol

Pre-approval (room temperature and accelerated storage conditions)

Inverted orientation

Accelerated temperature (pages 575-577).

Room temperature (pages 578-580).

Upright orientation

Accelerated temperature (pages 581-582).

Room temperature (pages 583-584).

Post-approval (room temperature storage conditions)

Inverted orientation (page 585-587).

Post-Approval Stability Commitment (page 588)

Analytical Procedures - Stability (pages 589-617)

Stability Data for batch #6403 including representative chromatograms from samples at 3 months test stations.

Accelerated storage conditions, inverted orientation (pages 620-621, 632-633).

Room temperature storage conditions, inverted orientation (pages 622-623, 628-629).

Accelerated storage conditions, upright orientation (pages 624-625, 634-635).

Room temperature storage condition, upright orientation (page 626-627, 630-631).

Expiration Dating Period

Based on the enclosed 3 months accelerated stability data, A.L. Laboratories proposes conditional 24 month expiration dating. This dating will be verified by 24 month room temperature data which will be filed annually as they become available, per our stability commitment.

Special Study: Single Spray Drug Content Comparison with Ventolin Inhalation Aerosol

A study was performed comparing single spray drug content of Albuterol Inhalation Aerosol (Salbutamol MDI) to Ventolin Inhalation Aerosol (pages 636-667). The results show Albuterol Inhalation Aerosol with the valve to be superior to Ventolin Inhalation Aerosol in regards to content uniformity of single sprays.

We trust that our responses fully address the Administration's concerns.

Sincerely,

A.L. Laboratories, Inc.

Deborah Winkel
Senior Director, Regulatory Affairs

DW/jb

Enclosures

F:\...\0824\SUBMISS\791DLRSP.LTR

BARRE-NATIONAL INC.

NAI
(d Trowbridge 8/4/93

July 26, 1993

Office of Generic Drugs
CDER, FDA
Attn: Roger L. Williams, M.D.
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

RE: Albuterol Inhalation Aerosol
ANDA #73-045
Notice of Change of Address

Dear Dr. Wiliams:

We would like to take this opportunity to inform you that the Regulatory Affairs group of Barre-National have relocated to the following address:

BARRE-NATIONAL INC.
Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500
Baltimore, Maryland 21224
Phone: (410) 558-7250
Fax: (410) 558-7262

While continuing to address all correspondences to my attention, please note of the above referenced address in effect as of July 12, 1993.

Sincerely,
BARRE-NATIONAL INC.

Deborah Winkel
Director, Regulatory Affairs

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A. L. LABORATORIES, INC.
One Executive Drive, P.O. Box 1399, Fort Lee, New Jersey 07024

May 7, 1992

ORIG NEW CORRES

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MAY 12 1992

GENERIC DRUGS

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Roger L. Williams, M.D.
MPN II, HFD-600
5600 Fishers Lane
Rockville, Maryland 20857

Re: Notice Of Change Of Ownership Of An Abbreviated New Drug Application

Dear Dr. Williams:

In accordance with 21 CFR 314.72, we wish to announce that Generics (U.K.) Limited has transferred to A.L. Laboratories ownership of the abbreviated new drug application for:

ANDA #73-045
Albuterol Inhalation 90 µg / Inhalation

Pursuant to 21 CFR 314.72, we hereby attach the following information:

1. Letter from former owner stating that all rights have been transferred to new owner.
2. Signed Form 356H from new owner.
3. Effective date of ownership change.
4. Statement about new owners' copy of application.

All future correspondence regarding this application should be directed to:

Deborah Winkel
Director, Regulatory Affairs
A.L. Laboratories, Inc.
7205 Windsor Blvd.
Baltimore, MD 21207

REGFILES\LETTERS\DEBBY\WILLIAMS.LTR

Telephone: 201 947-7774 • FAX: 201 947-5541

A. L. LABORATORIES, INC.
One Executive Drive, P.O. Box 1399, Fort Lee, New Jersey 07024

Please acknowledge receipt of this correspondence, by signing, dating, and returning the attached acknowledgement copy.

Sincerely,

Deborah Winkel
Director, Regulatory Affairs

DW/kvn

cc: Mr. R. Pudlak (A.L. Laboratories)
Mr. I. Jacobson (Generics (U.K.) Limited)
Mr. G. Barrett (Barre-National, Inc.)

REGFILES\LETTERS\DEBBY\WILLIAMS.LTR

Telephone: 201 947-7774 • FAX: 201 947-5541

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

April 26, 1991

NDA ORIG AMENDMENT
AC (Draft)

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 15C
7500 Standish Place
Rockville, Maryland 20855

ARCHIVAL COPY

SUBJECT: ANDA 73-045
Albuterol Inhalation Aerosol

Dear Dr. Williams:

Reference is made to your letter dated September 25, 1990 in which it was requested that draft labels and labeling, reflecting revisions made in the Ventolin labeling, be prepared and submitted for Albuterol Inhalation Aerosol.

In accordance with that request, we are herewith submitting revised draft labels and labeling distributed as follows: Four sets of labels/labeling are provided in the archival copy and one set of labels/labeling is provided in the review copy.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Mary-Anne D'Esposito for

Leon Lachman, Ph.D.
President

Enclosure

This letter knot reference
in the 7/12/91 letter but
this piece is also considered
placed in for letter
for [illegible]

RECEIVED
APR 29 19[illegible]
GENERIC DRUGS

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

January 2, 1991

73,045

(FEDERAL EXPRESS 1/2/91)

Dr. Marilyn N. Martinez
Food and Drug Administration
Office of Generic Drugs
(HFD 604)
Metro Park North
7500 Standish Way
Rockville, MD 20850

Dear Dr. Martinez:

Pursuant to our meeting at Metro Park North II on December 6, 1990, and our phone conversation of December 21, 1990, please find enclosed a statistical analysis comparing the results from the 1-Puff and 2-Puff dosage clinical studies performed as part of the submission to support ANDA #73-045 Albuterol Inhalation Aerosol of Generics U.K., Ltd. As was agreed in our phone conversation of December 21, 1990, this additional evaluation of the clinical studies submitted in support of the above referenced ANDA is not being submitted to the ANDA jacket, but as general scientific support of the significance of the 2-Puff vs. the 1-Puff doses. This submission approach was also agreed to by the FDA representatives present at the December 6, 1990 meeting.

The attached statistical analysis was performed by who was present at the December 6, 1990 meeting at the FDA and who is at the In his summary, states that "Statistical analysis lends unequivocal support for the sensitivity of FEV_1 as a measure of clinical response to increased dosages of inhaled Albuterol. Therefore, the demonstrated clinical equivalence in the submissions reflects clinical equivalence on sensitive measures between generic Albuterol and the two innovator formulations".

We will be sending you the additional general scientific information discussed at our December 6, 1990 meeting at the FDA.

Kind regards.

Sincerely,

Leon Lachman, Ph.D.
President

LL/lpa
Attachment
cc: W. Adams, Ph.D.
G. Burke, M.D.
S. Dighe, Ph.D.
R. Williams, M.D.

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

BIOAVAILABILITY MATERIAL

March 23, 1990

AMENDMENT

Bruce Burlington, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: ANDA 73-045
Albuterol Aerosol

Dear Dr. Burlington:

We are submitting at this time an amendment to the pending subject application which provides additional bioequivalency information for albuterol aerosol. Enclosed is the clinical report for a study entitled "Comparative, Two-way, Double-blind, Randomized Clinical Efficacy Study Comparing Generic Albuterol and Ventolin (R) Aerosols in Exercise-induced Asthmatics." This amendment includes a clinical summary, a copy of the study protocol, a statistical report, curriculum vitae of the principal investigator and clinical data for each subject.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Leon Lachman, Ph.D.
President

Enclosure

RECEIVED
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GENERIC DRUGS

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GENERIC DRUGS

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LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

November 21, 1990

(FEDERAL EXPRESS 11/21/90)

Dr. Marilyn N. Martinez
Office of Generic Drugs
(HFD 604)
Food and Drug Administration
Metro Park North
7500 Standish Place
Rockville, Maryland 20850

ORIG NEW CORR

Subject: Albuterol Inhalation Aerosol ANDA #73-045

Dear Dr. Martinez:

This is intended to follow up on our recent phone conversation at which we confirmed December 6, 1990. from 3 - 5 p.m. as the rescheduled time for the meeting requested in my letter of September 21, 1990, to Dr. Peck as agent for Generics U.K. Please advise location of meeting and those from the FDA who will be attending. The attendees for Generics U.K. Ltd. will be the same as listed in my letter of September 21, 1990, to Dr. Peck.

In accordance with your request, the following represents a tentative agenda for this meeting.

- Discuss the recommendations of the Pulmonary - Allergy Drugs Advisory Committee.

  + Design of Comparative Clinical Efficacy studies for metered dose inhalers that differed from those submitted in support of the above referenced ANDA and how they impact on the studies already performed and submitted.

  + The design which would compare generic vs. brand products by dose response and/or cumulative assay, doubling the dose until maximum response is attained.

  + The Committee's suggestion of how large a difference in effect would be considered clinically effective. The Committee recommended that the dose corresponding to 50% of the maximum effect be calculated from the data obtained with the new study design. The approval criteria was that the test product had to be within 50% of the innovator product. It is not clear whether this referred to differences in means or the confidence intervals. There was no definition of the Committee of acceptable ranges for the confidence intervals for duration and maximum FEVI.

- The implications of the Committee's recommendations on ANDA 73-045.
- Review status of clinical studies submitted in support of the ANDA 73-045.
- Review status of the chemistry and manufacturing data.

I appreciate your assistance in coordinating this meeting. I look forward to receiving from you a list of attendees from the FDA and location of the meeting that we agreed is to take place from 3 - 5 p.m. on December 6, 1990.

Kind regards.

Sincerely,

Leon Lachman

Leon Lachman, Ph.D.
President

LL/lpa
cc: G. Burke, M.D.
C. C. Peck, M.D.
S. Dighe, Ph.D.
R. Williams, M.D.

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because of processing procedures
of the time. wcb
5/2/94

ORIG

SUPERPHARM
CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

November 19, 1990

Sec 4/26/91 submission for labeling
6/11/92

Director, Division of Generic Drugs
Center for Drug Evaluation and Research
HFD-630, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-045
Albuterol Inhalation Aerosol,
0.09 mg/Actuation
Revised Labeling

Dear Sir:

Reference is made to the above listed abbreviated new drug application, and your letter of September 25, 1990 (a copy is enclosed). Your letter noted that the innovator, Glaxo, Inc., had recently revised their Ventolin labeling (revision date January 1989, approval date April 14, 1989).

We are presently submitting for your review and comment, revised draft labeling for Albuterol Inhalation Aerosol, 0.09 mg/ Actuation which is intended to reflect these changes.

Thank you for your attention in this matter, and we look forward to your response.

Sincerely yours,
SUPERPHARM CORPORATION

Herbert F. Luther Jr. (for)

James R. Beebe
Associate Director,
Regulatory Affairs

Enclosure

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

pc
NDA 073-045
AI FR2)

See 4/26/91 submission for labeling 6/11/92

July 5, 1990

D. Bruce Burlington, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: ANDA 73-045
Albuterol Inhalation Aerosol

Dear Dr. Burlington:

Reference is made to the Administration's letters dated June 26, 1989 and April 23, 1990 regarding additional information that would be needed in support of the subject application. An amendment dated August 28, 1989 was submitted in response to the June 26, 1989 letter.

We are submitting, at this time, an amendment which completes our response to the Administration's letter of June 26, 1989. In addition, our responses to the Administration's letter of April 23, 1990 are also attached. Each of the Administration's comments are reiterated, followed by our response to each of the comments. An Index which details the contents of this amendment immediately follows Form FDA 356h.

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Leon Lachman, Ph.D.
President

Enclosure

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

April 30, 1990

NDA ORIG AMENDMENT
AC

Bruce Burlington, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: ANDA 73-045
Albuterol Aerosol

Dear Dr. Burlington:

Reference is made to the Administration's letter dated September 19, 1989 requesting additional information regarding the in vitro test data submitted in support of the Albuterol Aerosol application. We are submitting at this time an amendment to the pending subject application which provides the requested information.

Our responses to each of the Administration's comments are outlined in the attached summary with supporting data included in the accompanying attachments.

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Leon Lachman, Ph.D.
President

Enclosure

RECEIVED
MAY 1 1990
GENERIC DRUGS

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES
1600 STEWART AVENUE
WESTBURY, NY 11590
(516) 222-6222
FAX (516) 683-1887

June 18, 1990

D. Bruce Burlington, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Attention: Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: ANDA 73-045
Albuterol Inhalation Aerosol

Dear Dr. Burlington:

Reference is made to a telephone conversation on Thursday, June 14, 1990 between Mr. Gordon Johnston of the Administration and Dr. Leon Lachman of Lachman Consultant Services, Inc. regarding the need to submit a revised Form FDA 356h and a revised letter appointing Lachman Consultant Services as Agent for Generics (UK) Limited, the holder of the subject application.

We are submitting, at this time, a revised Form FDA 356h which indicates that Generics (UK) Limited is the applicant. Also included is letter from Generics (UK) Limited appointing Lachman Consultant Services as their Agent in the United States.

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

If you should have any questions regarding the information in this submission, please do not hesitate to contact the undersigned at (516) 222-6222.

Sincerely,

Leon Lachman, Ph.D.
President

Enclosure

Desk Copy: Mr. Gordon Johnston, HFD-238

SUPERPHARM
CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

Orig

NDA ORIG AMENDMENT

August 28, 1989

Mr. Richard Terselic,
Acting Director
Division of Generic Drugs
Office of Drug Standards, CDER
Food and Drug Administration
HFD-230, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-045
ALBUTEROL INHALATION AEROSOL, 0.09 MG/INH
AMENDMENT TO A PENDING APPLICATION

Dear Mr. Terselic:

Reference is made to the Administration's June 26, 1989 letter regarding the above pending abbreviated new drug application.

Enclosed please find our responses to each of the letter's comments. An accopress binder entitled, "Test Methods for Validation" also accompanies this response. It includes, in triplicate, copies of all testing procedures required for the analysis of this finished dosage form.

Thank you for your prompt review of the submitted information and please do not hesitate to contact us if additional information is needed. Thank you.

Sincerely,

Diana Sloane

Diana Sloane
for Generics (UK) Ltd.
c/o Superpharm Corporation

DS/jgh

Enclosures

RECEIVED
AUG 29 1989
GENERIC DRUGS

SUPERPHARM CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

Orig

July 28, 1989

ORIG NEW CORRES

Mr. Richard Terselic,
Acting Director
Division of Generic Drugs
Office of Drug Standards, CDER
Food and Drug Administration
HFD-230, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

WAI 9PP 3/14/90

Re: ANDA 73-045
ALBUTEROL INHALATION AEROSOL, 0.09 MG/INH

Dear Mr. Terselic:

Reference is made to the above pending abbreviated new drug application and the Administration's June 26, 1989 letter regarding such.

This letter is to inform you that we have sent the following for analysis and review to the FDA laboratory in St. Louis, MO on July 24, 1989.

1. Albuterol: 1 x 50 grams
Lot No. 26SBM
Generics (UK) Ltd., Lot No. 6567D

Manufacturer: DMF No.

2. Albuterol USP RS

Attached is a copy of the letter sent.

Please do not hesitate to contact us if additional information is required.

Sincerely,

Diana Sloane

Diana Sloane
For Generics (UK) Ltd.
c/o Superpharm Corporation

RECEIVED
AUG 2 1989
GENERIC DRUGS

DS/jgh

Enclosures

SUPERPHARM
CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

Orig

June 23, 1989

Mr. Richard Terselic
Acting Director
Division of Generic Drugs/FDA
Office of Drug Standards
Center for Drug Evaluation and Research
HFD-230, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-045;
ALBUTEROL AEROSOL METERED INHALATION, 0.09 MG/INH

Dear Mr. Terselic:

Pursuant to 21 CFR §314.50 (d)(3) and in accordance with 21 CFR §320, the bioequivalence of the above proposed drug product will be supported through the submission of a completed clinical efficacy in-vivo ONE-PUFF bioequivalence study. This ONE-PUFF study supplements the TWO-PUFF clinical study submitted to this application on May 16,1989. The parameters and 27 subjects used in this ONE-PUFF study were also used in the previously submitted 42 patient TWO-PUFF study.

Enclosed please find the completed three-way clinical efficacy ONE-PUFF bioequivalence study comparing the drug product which is the subject of this Application and both U.S. pharmaceutical alternatives of the listed drug, i.e., PROVENTIL (Schering) and VENTOLIN (Glaxo).

Please note that the clinical work for the study was done in the [ ] under the supervision of [ ]

The results and the statistical analyses included in the report are by [ ] A summary of the statistical data interpretation as presented by [ ] is found in the study.

Included for your consideration is the following:

1) The completed clinical efficacy in-vivo ONE-PUFF bioequivalence study (3 volumes) entitled "Comparative, 3-way Double-Blind Randomized Clinical Efficacy Study Between Albuterol (Generics (U.K.) Ltd.) Proventil® (Schering Inc. U.S.A.) and Ventolin® (Glaxo Inc., U.S.A.) 90 mcg Metered-Dose Albuterol Inhalers (One-Puff Study)."

2) Formulation Information for the drug product which is the subject of this application; Albuterol Aerosol Metered Inhalation, 0.09 mg/INH (Generics (UK) Ltd.).

3) Draft package insert and patients instructions for use.

4) Note that a comparative spray pattern study and in-vitro test data for the subject drug product; Albuterol Aerosol Metered Inhalation 0.09 mg/INH, and the brand alternatives; PROVENTIL (Schering) and VENTOLIN (Glaxo) was previously submitted for review as volume 1.3 with the original application on December 23, 1988.

5) Note also that a clinical efficacy in-vivo TWO-PUFF bioequivalence study was also previously submitted to this pending application on May 16,1989.

Sincerely,
SUPERPHARM CORPORATION

Diana Sloane

Diana Sloane
Associate Director,
Regulatory Affairs

DS/jl

Enclosures

SUPERPHARM CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

ORIG NEW CORRES

[illegible] AVAILABILITY MATERIAL

May 16, 1989

Dr. Marvin Seife, Director
Division of Generic Drugs/FDA
Office of Drug Standards
Center for Drug Evaluation and Research
HFD-230, Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 73-045;
ALBUTEROL AEROSOL METERED INHALATION, 0.09 MG/INH

Dear Dr. Seife:

Pursuant to 21 CFR §314.50 (d)(3) and in accordance with 21 CFR §320, the bioequivalence of the above proposed drug product will be demonstrated through the submission of a completed clinical efficacy in-vivo bioequivalence study. Enclosed please find a completed three-way clinical efficacy bioequivalence study comparing the drug product which is the subject of this Application and both U.S. pharmaceutical alternatives of the listed drug, i.e., PROVENTIL (Schering) and VENTOLIN (Glaxo).

Please note that the clinical work for the study was done in the

under the supervision of

The results and the statistical analyses included in the report are by

. A summary of the statistical data interpretation as presented by is found in the study

Included for your consideration is the following:

1) The completed clinical efficacy in-vivo bioequivalence study (4 volumes) entitled "Comparative, 3-way Double-Blind Randomized Clinical Efficacy Study Between Albuterol (Generics (U.K.) Ltd.) Proventil® (Schering Inc. U.S.A.) and Ventolin® (Glaxo Inc., U.S.A.) 90 mcg Metered-Dose Albuterol Inhalers."

2) Formulation Information for the drug product which is the subject of this application; Albuterol Aerosol Metered Inhalation, 0.09 mg/INH (Generics (UK) Ltd.).

3) Draft package insert and patients instructions for use.

4) Please note that a comparative spray pattern study and in-vitro test data for the subject drug product; Albuterol Aerosol Metered Inhalation 0.09 mg/INH, and the brand alternatives; PROVENTIL (Schering) and VENTOLIN (Glaxo) was previously submitted for review as volume 1.3 with the original application on December 23, 1988.

Sincerely,
SUPERPHARM CORPORATION

Diana Sloane

Diana Sloane
Associate Director,
Regulatory Affairs

DS/rb

Enclosures

SUPERPHARM
CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

Orig

March 6, 1989

Dr. Marvin Seife, Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation & Research
HFN-230, Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

AMENDMENT

Re: ANDA 73-045
ALBUTEROL AEROSOL INHALER, 90 MCG
AMENDMENT TO A PENDING APPLICATION

Dear Dr. Seife:

Reference is made to the above pending abbreviated new drug application submitted on December 23, 1988 by Superpharm Corporation for Generics (UK) Ltd.

We hereby submit for review additional information concerning several Drug Master Files referenced in the above application. These DMFs were previously referenced by their submission dates and we now have obtained the assigned DMF numbers and wish to provide them:

a) DMF
A copy of the FDA DMF letter and the DMF authorization letter submitted previously are attached.

b) DMF
A copy of the FDA DMF letter and the DMF authorization letter submitted previously are attached.

c) DMF
An updated DMF authorization letter is attached.

We also would like to take this opportunity to correct a typographical error in the title of page 339 of our original application. An updated copy of page 339 is attached.

Thank you for your prompt review of the submitted information. Please do not hesitate to contact us if additional information is needed.

Sincerely,
SUPERPHARM CORPORATION

Diana Sloane

Diana Sloane
Associate Director,
Regulatory Affairs

DS/jgh

Enclosures

Bio (orange)

info is acceptable
11/5/89 for
DOK

SUPERPHARM
CORPORATION

1769 Fifth Avenue / Bayshore, New York 11706 / 516-434-4800
Fax: 516-434-3188

December 23, 1988

Dr. Marvin Seife, Director
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation & Research
HFN-230, Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: ALBUTEROL AEROSOL INHALER, 90 MCG
ORIGINAL APPLICATION

Dear Dr. Seife:

On behalf of Generics (UK) Limited of Station Close, Potters Bar, Herts EN6 1TL, England, we hereby submit at this time an Abbreviated New Drug Application for Albuterol Aerosol Inhaler, 90 mcg. The holder of this application, Generics (UK) Ltd., has been producing this drug product in the United Kingdom for sale over three years and it currently is approved and in distribution in 10 countries. Superpharm Corporation has been designated as Generic (UK) Ltd.'s U.S. agent for this new drug application which is submitted pursuant to 21 U.S.C. 355 (Federal Food, Drug and Cosmetic Act, as amended) and in accordance with 21 CFR §314.55. All correspondence regarding this application should be directed to Superpharm Corporation who will act with and on behalf of Generics (UK) Ltd. to promptly provide any additional information desired with regard to this application's review. A letter authorizing Superpharm Corporation as the U.S. agent may be found directly following the required 356h form.

The completed and signed Form 356h immediately follows this letter. Information required by 21 CFR §314.50(a) is contained on that form. Samples required by 21 CFR §314.50(e)(i) will be submitted upon requests; a listing of what samples will be supplied is found in Item 12 of this Application.

The Methods Validation Package required by 21 CFR §314.50(e)(2)(i) accompanies this Application as a separate accopress binder.

The bioavailability/bioequivalence information required by 21 CFR §314.50(d)(3) to be forwarded under separate cover to the Application is found in Volume 1.3 of this Application.

Information required by 21 U.S.C. §355(j)(2)(A) is found in the following Application Items:

Subsection	Application Vol/Item
(i) Conditions of use	1.1/2
(ii) Active Ingredients	1.1/2
(iii) Route of Administration	1.1/2
(iv) Bioavailability/Bioequivalence	1.3
(v) Labeling	1.1/3
(vi) Manufacturing & Controls	1.1/7
(vii) Labeling & Samples	1.2/12
(viii) Patent Certification	1.1/2
(ix) Method of Use Patent Information	1.1/2

The Archival copy of this Application consists of three volumes, designated as Volumes 1.1, 1.2 and 1.3

The Review copy of this Application consists of three volumes, designated as Volumes 1.1, 1.2 and 1.3

Thank you for your prompt review of the submitted application.

Sincerely,
SUPERPHARM CORPORATION

Diana Sloane

Diana Sloane
Associate Director,
Regulatory Affairs

DS/jgh

Enclosures